UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/211,715	12/14/1998	FAHAD AL-OBEIDI	P-SE-3243	9543

23601 7590 11/20/2002

CAMPBELL & FLORES LLP
4370 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122

EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	24

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/211,715	AL-OBEIDI ET AL.
Examiner	**Art Unit**
Samuel W Liu	1653

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,7-11,20-23 and 25* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,7-11,20-23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other .

DETAILED ACTION

The response filed 10 October 2002 (paper 23) has been received and entered. Amendments of Claims 2, 3, 21 and 22, cancellation of Claims 4-6, 24and 26, and the extension for three months have been entered. Claims 2, 3, 7-11, 20-23 and 25 are pending to which the followings are or remain applicable. Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Objection to Claim

The disclosure is objected to because of the following informalities:

Claim 10 recitation "-Pal(3)Me" appears misspelling. Since the specification has defined "PalMe(3)" that refers to as β-(3-N-methylpyridinium)-alanine, change to PalMe(3) is advised.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 3 (currently amended) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for Y-I-R containing peptides or closely related analogues, does not reasonably provide enablement for a general formula claimed and its utilization. The specification does not enable a skilled in the to which it pertains, or with which it is most nearly concerned, to make and use the commensurate in scope with these claims.

In this regards, the application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998) as to undue experimentation. The factors include: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) The nature of the invention

Claims 2 and 3 (currently amended) recite very diverse formula A1-A2-$(A3)_m$ –B. The method of the current application for inhibiting Xa protease activity largely depends on specificity toward Xa protease. Because the method of the current application relies on the compound of claim 2, the method encompasses variables with regard to specificity and potency of Xa inhibition peptide analogue.

The specification of the instant application sets forth that all the synthesized peptides contain at least one a common core structure, *e.g.*, Y-I-R (Tyr-Ile-Arg) or functional equivalents thereof, and are capable of specially inhibiting factor Xa activity [see abstract, page 5, line 15-17, page 8 line 20-23 and "Summary of the Invention" (page 5-6)]. The Y-I-R motif is therefore a consensus motif (common core) for Xa inhibition. Example XXXVI provides evaluation of inhibiting Xa activity by compounds containing Y-I-R and closely related structural derivatives thereof. The specification teaches: 1) the invention is directed to Y-I-R peptides in which the Y-I-R motif determines both specificity and efficacy of the peptides (see page 8, lines 9-12); and 2)

the inheritance of the specificity of inhibiting factor Xa within the Y-I-R motif (see page 8, lines 20-23). The claims, however, recite a broad formula (see Claims 2 and 3) encompassing numerous substitution combinations, which are very divergent from the consensus Y-I-R motif disclosed in the specification. Since the claims are directed to the formula (genus) encompassing very broad range of peptide compounds, the scope of enablement is not commensurate with the scope of claims.

2) The breadth of the claims

The instant claims do not recite the consensus motif critical to Xa inhibition. Instead, claims are broadly drawn to a multitude of compounds derived from a general formula A1-A2-$(A3)_m$–B, which encompass a multitude of unrelated chemical moieties or groups, while the specification discloses the Y-I-R containing structures and their uses. Thus, scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

3) The unpredictability

There is an unpredictable degree of diversity from the consensus motif Y-I-R, and the peptidic inhibitors deviated from the consensus motif are highly variant. Thus, the invention is unpredictable in the absence of factual indicia to the contrary.

4) The amount of direction or guidance presented

The instant specification presents only limited guidance for the peptidic analogues comprising the consensus Y-I-R motif and their functional assays. Noticeable is that all potential candidates having Xa inhibitory activity possess the consensus motif or the motif-like core structure (see Example XXXVI and Table 3). It is apparent that structures deviating from

inherent motif Y-I-R would require guidance with respect to the inhibition selectivity and potency. The general formula A1-A2-$(A3)_m$ –B recited in claims 2 and 3 includes numerous structural variants. According to the claim language, *e.g.*, claim 2 recitation of "R_2 is .... Independently selected from...", many of the claimed compounds are non-amino acid compounds, which are resulted from *substituting* $R_{2A}R_{2B}$ (in $CR_{2A}R_{2B}$), $R_{5A}R_{5B}$ (in $CR_{5A}R_{5B}$) and $R_{8A}R_{8B}$ (in $CR_{8A}R_{8B}$) (see claims 2 and 3) *with* carbon-containing chemical groups (note that amino acid requires alpha carbon to be bonded to an amine group ($-NH_2$), a carboxyl group (-COOH), and a hydrogen atom; replacement of the hydrogen will generate non-amino acid derivative). Because the current invention is directed to compound that has the structure X_1–Y-I-R–X_1 and specifically inhibit Xa activity (see "summary of the invention at page 5, lines 13-25), whether the non-amino acid compound as above-mentioned have Xa inhibition activity is unpredictable and require undue experimentation. The specification provides no guidance and working example(s) for this regard. Considering amino acid derivative, whether alteration of side chain of amino acid residue would still retain activity comparable to the Y-I-R motif containing peptidic are also unpredictable in view of structure-function relationship. It has been reported that substitution mutation in Xa inhibition protein or peptide, *e.g.*, change of Arg at position 34 to any amino acid residue (except lysine) within antistasin, a specific Xa inhibitor, abolish the inhibitor activity (see Hofmann K. J. *et al.* (1992) *Biochem. J.* 287, 943-949), suggesting altering residue side-chain has a great impact on the activity.

5) The quantity of experimentation necessary:

In the absence of working examples with regard to the above mentioned numerous variant sequences, the unpredictability of the art, the lack of sufficient guidance in the

specification, and the breadth of the claims, it would take undue trial and error to practice the claimed invention. Because of the reasons forgoing, the quantity of experimentation would be large and unpredictable because the skilled artisan would have been required to carry out a large body of tests for screening and making any variant(s) that is (are) of desirable inhibitory activities against Xa protease without a prior expectation of success.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art a Ph.D. with several years of experience do not supplement the omitted description with respect to a massive number of variant sequences of polypeptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least an organic chemist or a biochemist with several years of experience in protein manufacturing as well as knowledge in organic synthesis, peptide chemistry, enzymology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

The variant polypeptides or peptides may fall into unanticipated or/and abolished activities (see the Hofmann *et al.* reference). Hofmann *et al.* show that substitution of Arg (34) with other amino acid residue (except Lys residue) results in a dramatic decrease of inhibitory activity (*i.e.*, increase IC_{50} (nM) value) of antistasin, a Xa-inhibition protein. In order to maintain a reasonable inhibitory spectrum, the skilled artisan are required high level of skill in order to identify clones that generate the desirable peptides of specific Xa-inhibiting activities.

The present claims recite a very broad formula (Claims 2 and 3) that encompasses a large number of substitution combinations diverse from the consensus motif disclosed in the specification. This would not allow the artisan to practice the invention because the vital

consensus motif is not inherent in claims. Note that the consensus sequence contributes to selectivity or/and potency of peptidic compounds against Xa protease.

In consideration of each of factors stated above, there is undue experimentation because of variability in prediction of outcome that is not addressed by the instant application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Applicant's response filed October 10, 2002 (pages 9-20) with respect to the rejection under 35 USC 112, the first paragraph in the prior Office action has been fully considered but they are unpersuasive.

Applicants assert that there is no evidence or reason to show that any deviation from the Y-I-R motif would automatically result in less selectivity (see page 10, the third paragraph, lines 3-6) and that there is no objective evidence to support the proposition that variation from the Y-I-R motif necessarily results in decreased activity (see page 11, lines 9-11). This is found unpersuasive for the reasons stated in the following.

(i) Ostrem, J. A. *et al.* (*Biochemistry* (1998) 37, 1053-1059) show a series of low molecular weight peptide inhibitors of factor Xa, which is identified by screening a combinatorial peptide library composed of L-amino acids. Ostrem *et al.* teach that the minimal inhibitory sequence is a tripeptide, L-tyrosinyl-L-isoleucyl-L-arginyl (i.e., Y-I-R) which potently inhibits factor Xa activity. Also, Ostrem *et al.* demonstrate that deviation from the Y-I-R consensus motif results in dramatically decrease of the inhibitor activity against Xa protease (see especially Table 2 data at page 1056).

(ii) The specification *per se* supports the Y-I-R consensus motif (see Example XXXVI, wherein all the compounds contain the Y-I-R or Y-I-R like (structurally functionally) consensus structure).

Applicants infer that there is likely to be some change in selectivity of inhibiting Xa protease and whether there is increase or decrease in such selectivity can be determined by experimental data shown in Example XXXVI of the specification (see page 10, the last two sentences). In fact, what are shown in Example XXXVI do not support the applicant's inference. It should be noted that instead of reciting K_i value to each compound, all the listed compounds in Example XXXVI have a very broad range from 100 μM (10^{-4} M) and 1 pM (10^{-12} M). Thus, the data provided by Example XXXVI cannot be sued to evaluate whether there is an increase or decrease of the compound activity, *e.g.*, specificity. On the contrary, the data of Example XXXIV has a bearing on the importance of Y-I-R consensus motif since most compounds as listed in the Example have the motif with some "functionally modified from the motif, *e.g.*, hydrophobic Ile (I) change to other hydrophobic group, *e.g.*, 1-naphthylalanine (Nal).

The applicants further assert that Example XXXXVI is a working example teaching the peptide compounds that have K_i values between 100 μM (10^{-4} M) and 1 pM (10^{-12} M) for factor Xa inhibition, and that despite the deviation from the Y-I-R motif, the compounds maintain Xa inhibitory activity, and some of the compounds show even greater activity (see page 11, lines 1-9). The assertion is not persuasive because (i) a remarkable wide range of K_i values (10^{-4} M to 10^{-12} M) that represents 10^8 different deviation of the inhibitory constant values (K_i). Thus, the data presented in Example XXXXVI do not explicitly asses the Xa inhibition activity for each compounds listed in the example (see Table 3); and (ii) because the data presented in Example

XXXVI *per se* does not address increase or decrease of Xa inhibition activity with regard to each compound and because nowhere in the specification sets forth a standard with which the increase or decrease of K_i values can be compared, the inference of "some of the compounds show even greater activity" cannot be drawn.

The response asserts that claims 2 and 3 are directed to compound comprising Y-I-R motif, or closely related analogues (see the third paragraph at pgae11) *e.g.*, R_2 is 4-hydroxyphenylmethyl (see page 12); R_5 is 2-butyl (see page 15); and R_8 is 3-guanylpropyl (see page 16). The assertion is not persuasive because resultant peptide with the above-stated R_2, R_5, and R_8 substitutions does not generate Y-I-R peptide but rather non-amino acid analogue. For instance, the substitution at R_5 with 2-butyl would give rise to [...-HN-CH_2–CH (CH_3)–CH_2–CO-...] which is an isobutyl derivative but not isoleucine residue.

The response asserts that one skilled in the art would recognize a common feature of the constituents at position R_8, namely, the presence of a moiety with a positive charge (see pages 18, lines 1-3). This is found unpersuasive because (i) the compounds having the amine-based positive charge(s) shown on page 17 are far divergent from arginine structure at R_8, and do not have a common feature Y-I-R; thus, the skilled artisan cannot envision such the constituents and any moiety with positive charge(s); (ii) because Arginine (R) of the Y-I-R motif targets the factor Xa's active site pocket (see page 1053, the last paragraph of the Ostrem *et al.* reference), any structural modification away from arginine residue in the motif would greatly affect specificity and potency of Xa inhibitory compounds.

Applicants argue that there is an unpredictable degree of diversity from Y-I-R core structure and Example XXXVI provides factual indicia that structures of the present application

with deviation from the Y-I-R motif have Xa inhibition activity (see the third paragraph, page 18). The argument is unpersuasive. Example XXXVI does not provide actual K_i values for each cited compounds (see the relevant forgoing statement) but rather recites very broad range of K_i values (*i.e.*, 100 μM – 1 pM). Thus, Example XXXVI gives no valuable input on bearing of the assertion that structural deviation from the Y-I-R motif still retains significant Xa inhibition.

In addition, applicants argue that the Hofmann *et al.* reference is not relevant to the present disclosure because Arg(34) in antistasin, an Xa inhibitor, disclosed by Hofmann *et al.* does not contain Y-I-R motif, and argue that length of antistasin protein differs from those of peptide compounds of the present application. Applicants further assert that Example XXXVI refuses the conclusion drawn from Hofmann *et al.* which states that alternating critical amino acid residue(s) would considerably decrease or abolish the activity of the studied polypeptide (see page 19). The argument and assertion are found unpersuasive (for the reasons, see the following).

Hofmann *et al.* reference is recited for factual indicia regarding how change of an amino acid reside in a Xa inhibition polypeptide will have a dramatic impact on the functional activity of the polypeptide. Please note that the Hofmann *et al.* reference is not necessary a prior art against the disclosure of the current application but rather is the art that addresses how structural alteration at a single residue results in decrease in activity is unpredictable in view of structure-function relationship. This is further is supported from the data showing the other single mutation at position 90 in Hofmann protein considerably reduces potency of inhibiting Xa activity (see Figure 6). Therefore, the reference teaches that it is not predictable on how substitution of residue(s) in a Xa inhibition polypeptide still maintains a reasonable inhibitory

potency of the polypeptide. As for the length concerned, it is not the subject issue here because Hofmann protein represents the other type of Xa inhibitor which des not necessarily have Y-I-R motif. Thus, the conclusion drawn from the Hofmann study is properly pursuant to addressing enablement requirement in the prior Office action.

Additionally, it is noted that the specification sets forth the peptides of the current invention can be between about 2 to 43 residues (see page 5, the third paragraph).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3, 9 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite as to the recitation "Leu-OH" (see the line 4 from the bottom of page 4 of the response); the recitation is not clear regarding whether or not the hydroxyl group is linked to alpha carbon of leucine. See also claims 3, 9 and 11.

Applicant's comments (pages 17-18) in the response filed October 10, 2002 has been fully considered but they are unpersuasive. Applicants assert that in the present case, Leu-OH is a notation used to emphasize that the C-terminus of the leucine is not modified (see page 22, lines 1-2). Note that leucine C-terminus is a carboxyl group as being a structural as well as a functional group, which is unbreakable, *e.g.*, broken down to a "subgroup" –OH (hydroxy). Given that hydroxyl group is linked to alpha carbon of the leucine residue, the molecule will

become 2-amino-4-methylpentanol rather that 2-amino-4-methylpentanic acid, *i.e.*, leucine. Furthermore, indication of free carboxyl group at C-terminus of leucine would be clear for identifying that the leucine residue is free from chemical modification.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The Claims 2-3 are rejected under 35 U.S.C. 102 (e) as anticipated by or, in the alternative as obvious under 35 U.S.C. 103(a) over Brunck T. K. *et al.* (US Pat. No. 5739112). Although the invention is not identically disclosed or described as set forth in 35 U.S.C. 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a designer having ordinary skill in the art to which said subject matter pertains, the invention is not patentable.

Although Brunck *et al.* do not set forth the general formula A_1–A_2–(A_m)-B in the instant application, US Pat. No. 5739112 discloses compounds that read on the said formula (see "preferred compound" set forth in lines 63-65 at column 8, also see column 9, Claims 1-10 and Tables 1-2). The disclosed compounds are potent and specific inhibitors of mammalian factor Xa protease (see Abstract and columns 1-5 and 8). For instance, $\underline{R_4}$ (alkyl of 2 carbon atoms) reads on R"$_1$ acetyl group (page 3 of the response) [*note that the underlined character indicates the recitation from the Brunck et al. reference (see column 9), whereas the non-underlined is from the current application disclosure*]; $\underline{R_3}$ (aryl of 6-14 carbon) reads on R_2 2-naphthylmethyl

group (pages 3 and 6 of the response); $\underline{R_2}$ (aralkyl or alky) reads on R_5 phenyl group (pages 6 and 4 of the response); and $\underline{R_1}$ (5-guanidinopentanal) reads on R_8 arginine side chain group, *i.e.*, 3-guanylprogyl (pages 4 and 6 of the response). Thus, the subject matter claimed in the instant application would have been anticipated if not obvious to one of ordinary skill in the art.

The comments in the response filed 10 October 2002 have been considered (see Pages 24-26). But they are unpersuasive.

Applicants assert that claim 2 and amended claims 3 do not read on Brunck since Brunck is directed only to dipeptide while claims 2 and 3 of the present application are directed to at least three to five amino acid residues in length (see page 24, the second paragraph). Applicants are referred to see formula I (column 8) which displays three residue peptide.

Based on comparison of Brunck's invention with Applicants' disclosure, applicants infer that Brunck *et al.* do not anticipate the present disclosure (see page 25 of the response). Applicants' argument is unpersuasive. The season for this has been set forth in the foregoing rejection.

Claim Rejection –Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Claims 2, 3, 8-10, 21-23 and 25 are rejected under the judicially created doctrine of the obviousness-type double patenting of the claim in US Pat. No. 5849510. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of US Pat. No. 5849510 discloses the identical formula as that of Claim 2 of the instant application. Claim 1 (5849510) and Claim 2 (the instant application) disclose the same formula and each R group of claim 1 of US Pat. No. 5849510 reads on the corresponding group of claim 2 of the instant application; thus, the claim 1 is an obvious variation of claim 2 of the present application. See also Claims 1 and 17 of US Pat. No. 5849510 *versus* the instant application Claim 3.

Claim 23 of US Pat. No. 5849510 is an obvious variation of claims 8 and 10 of the instant application because the compounds set froth in the patented claim 23 read on those of the application claims 8 and 10.

Claim 22 of US Pat. No. 5849510 is an obvious variation of claim 9 of the instant application because groups A1, A2, A3 and B of claim 22 read on the compound, *e.g.*, Ac-pAph-Chg-Arg-Leu-OH of the application claim 9, wherein group B is an (one) amino acid, *i.e.*, Leu).

Claim 24, SEQ ID NO: 279 (Ac-pAph-Chg-PalMe(3)-L-P-NH_2) and the compound Ac—pAph-Chg-PalMe(3)-NH_2 of US Pat. No. 5849510 read on the compound recited in claims 21 and 22 of the instant application, respectively.

Claim 40, SEQ ID NO:122 (Ac-pAph-Chg-R-L-P-NH_2) of US Pat. No. 5849510 reads on the compound recited in claim 23 of the instant application.

Claims 36-37 of US Pat. No. 5849510 disclose the same method as that of claim 25 of the instant application with respect to specific inhibition of the factor Xa activity.

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

It is noted that the current response filed 10 October 2002 has not addressed issue of the obvious-type double patenting rejection.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Karen Cochrane Carlson (Ph.D)

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

SWL

November 15, 2002